An Efficient Transformation of Cyclic Ene-carbamates into ω-(*N*-Formylamino)carboxylic Acids by Ruthenium Tetroxide Oxidation

Mamoru KANAME, Shigeyuki YOSHIFUJI, and Haruki SASHIDA*

Faculty of Pharmaceutical Sciences, Hokuriku University; Kanagawa-machi, Kanazawa 920–1181, Japan.
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The ruthenium tetroxide (RuO_4) oxidation of cyclic ene-carbamates resulted in the *endo*-cyclic carbon–carbon double bond cleavage to afford the corresponding ω-(*N*-formylamino)carboxylic acids in good yields. Substituted cyclic ene-carbamates derived from (3*R*)-3-hydroxypiperidine hydrochloride were converted into the *N*-Boc 4-aminobutyric acids by utilization of the RuO_4 oxidation as the key step, which were further transformed into (3*R*)-4-amino-3-hydroxybutyric acid, an important key intermediate for the synthesis of L-carnitine.

Key words RuO_4 oxidation; cyclic ene-carbamate; *endo*-cyclic carbon–carbon double bond cleavage; L-carnitine

The high-valent metal-promoted oxidation of a carbon–carbon double (C=C) bond with cleavage is a promising synthetic route to the corresponding carbonyl compounds. This chemistry has been extensively studied.[1] Ruthenium tetroxide (RuO_4) is well known as a highly effective oxidant,[2—4] and the oxidative cleavage of simple C=C bonds is one of the most common reactions between RuO_4[2] and alkenes. However, only a low effort regarding the oxidative cleavage of the C=C double bond to the corresponding carbonyl compounds in enol ethers, enol esters and enamines has been made to date. To the best of our knowledge, there are only two papers. The first example of this type of reaction was described by Desai and co-workers,[5] who reported one case that attempted the cleavage of a C=C bond in steroidal enamines. Torii and co-workers[6] revealed the procedure for the RuO_4 oxidative cleavage of enolic olefins including two six-membered nitrogen-containing heterocyles that afforded the carbonyl compounds under the conditions using the substrate in a suspension of CCl_4 and H_2O in the presence of $RuO_2 \cdot xH_2O$ and $NaIO_4$.

On the other hand, we have been working on the transformation of cyclic[7—9] and acyclic[10—12] *N*-acyl amines into the corresponding lactams and imides including the natural products[13—17] by the RuO_4 oxidation. The double layer oxidation method using a catalytic amount of RuO_2 hydrate, an excess of a $NaIO_4$ aqueous solution and ethyl acetate system was established for these purposes in our laboratory. In addition, it was recently reported that the single layer RuO_4 oxidation[18] of cyclic *N*-acyl amines using a *tert*-butanol and $NaIO_4$ aqueous solution system gave the ring opened ω-amino acids (Chart 1). We now report that the simple RuO_4 oxidation of various cyclic ene-carbamates including the optically active one into the corresponding ω-(*N*-formylamino)carboxylic acids and the formal synthesis of L-carnitine as the utilization of this RuO_4 oxidation.

Results and Discussion

The substrates, five-, six- and seven-membered cyclic ene-carbamates (**1a**, **2a**, **3a**), were prepared from the corresponding *N*-acyl amines *via* the *N*-acyl lactams in good yields by the reported method.[19] We have previously tested the utility of the urethane type *N*-protecting groups,[9] benzyloxycarbonyl (Z), *p*-nitrobenzyloxycarbonyl (PNZ), trichloroethoxycarbonyl (Troc) and *tert*-butoxycarbonyl (Boc) groups for the RuO_4 oxidation of the cyclic amines, and found the following three points: (1) the Z group is decomposed by RuO_4 that produced a low yield of products, (2) the PNZ and Troc groups generally require a longer reaction until the starting materials disappear, and (3) the Boc group is stable, accelerates the oxidation, and affords the products in high yields. In addition, the Boc group can be easily removed from the *N*-protected amines by common procedures. Thus, we selected the Boc group as the *N*-protecting group for this RuO_4 oxidation.

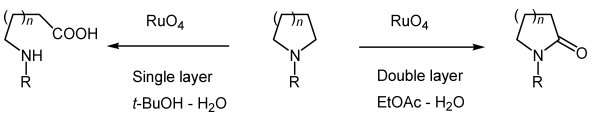


Chart 1

RuO_4 Oxidation of Ene-carbamates The oxidation of *N*-*tert*-butoxycarbonyl (Boc) pyrroline (**1a**) with RuO_4 using the established conventional double layer system of ethyl acetate and 10% $NaIO_4$ as a co-oxidant at 0 °C resulted in the successful *endo*-cyclic C=C bond cleavage to afford the desired ω-(*N*-formylamino)propanoic acid (**1b**) in 86% yield (Table 1, entry 1). The results obtained using several cyclic ene-carbamates are also summarized in Table 1. Six- (**2a**) and seven-membered cyclic ene-carbamates (**3a**) were also converted to the corresponding ω-(*N*-formylamino)carboxylic acid (**2b**, **3b**) in 78 and 90% yields under the same conditions, respectively (entries 2, 3). Next, this RuO_4 oxidation of the ene-carbamates was employed using the optically active amine frameworks. The five-membered *N*-Boc enamine (**4a**)[20—22] having the methyl ester moiety at the C-2 position was oxidized under similar conditions to afford the optically active *N*-formylamino carboxylic acid (**4b**) in 87% yield without any loss of chirality of the starting enamine **4a** (entry 4). A similar C=C bond cleavage oxidation of the optically active six-membered enamine **5a**[23] also proceeded to give the *N*-formyl derivative **5b** in 74% yield (entry 5). This oxidation was also successfully applied to the transformation of the phosphonic diester. The *N*-Boc five-membered aminophosphonic acid diester (**6a**) was similarly converted into the ω-(*N*-formylamino)carboxylic acids having a phosphonic diester moiety in 80% yield (entry 6).

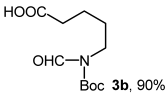
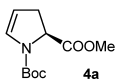
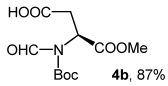
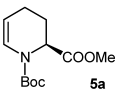
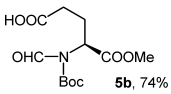
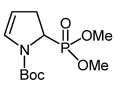
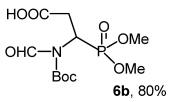
Synthesis of L-Carnitine Finally, we describe the formal asymmetric synthesis of L-carnitine from the commercially

* To whom correspondence should be addressed. e-mail: h-sashida@hokuriku-u.ac.jp

available (*R*)-hydroxypiperidine hydrochloride as the starting material by using the RuO_4 oxidation of both the *N*-acyl cyclic amines and enamines as two of the key steps (Chart 2). In recent years, carnitine and its analogues have attracted much attention because they have important biological activities.[24,25] Few synthetic studies[26] including asymmetric syntheses, the utilization of chiral starting materials, chemical resolution, enzymatic or microbial techniques, *etc.*, have been reported. The acetylation of *tert*-butyl (3*R*)-3-hydroxypiperidine-1-carboxylate (**7**),[27] prepared from (*R*)-hydroxypiperidine hydrochloride, with Ac_2O in pyridine gave the 3-acetyl derivative (**8a**) in 96% yield. 3-(*tert*-Butyldimethylsilyloxy)piperidine (**8b**) was obtained by the reaction of **7** and *tert*-butyldimethylsilyl chloride and imidazole in dry DMF in 97% yield. The first RuO_4 oxidation of the *O*-protected *N*-Boc piperidines (**8a**, **8b**) resulted in the carbonylation at the C-6 position to give the desired 5-acetoxypiperidones (**9a**) and 5-silyloxypiperidone (**9b**), together with the C-2 oxidative compounds (**10a**, **10b**) in the yields shown in Chart 2. The 5-acetoxy (5-silyloxy)piperidones (**9**) and 3-acetoxy(3-silyloxy) derivatives (**10**) could be separated by silica gel chromatography, and both structures of the products were determined by satisfactory spectroscopic (MS, IR, ^{1}H- and ^{13}C-NMR) measurements. In the case of the former **9a**, the 5-H signal appeared at δ 5.21 as a multiplet in the ^{1}H-NMR. The 3-H signal of the latter **10a** was observed at δ 5.31 as double-doublets in the lower field due to the deshielding effect of the carbonyl group at the C-2 position. The major compounds **9** were converted into the corresponding ene-carbamates (**11**) by the reported method,[19] which was reduction of the lactam carbamate with Super-Hydride, followed by *in situ* dehydration with trifluoroacetic anhydride (TFAA) and diisopropylethylamine (DIPEA). The 3-acetoxy (**11a**) and 3-silyloxy-1,2,3,4-tetrahydropyridines (**11b**) were obtained from the corresponding lactams (**9**) in 71 and 82% yields, respectively. Next, the second RuO_4 oxidation of the ene-carbamates (**11**) was carried out. The RuO_4 oxidation for the *endo*-cyclic C=C bond cleavage of the tetrahydropyridines (**11**) under our established conventional double layer system gave the desired ring-opening *N*-formylaminocarboxylic acids (**12a**, **12b**) in 80 and 78% yields. The hydroxylation of the 3-acetate (**12a**) with 2 M HCl, followed by the desalting with ion-exchange chromatography (Dowex 50W×8, 2% NH_4OH) produced the free (3*R*)-4-amino-3-hydroxybutyric acid (**13**) in 80% yield. Similarly, the free amino acid (**13**) was obtained from the 3-silyloxy derivative (**12b**) in 85% yield. **13** was identical to the authentic sample,[28] and was the key compound for the formal synthesis of L-carnitine (**15**).

In conclusion, RuO_4 oxidized the carbon–carbon double bond of several cyclic ene-carbamates to give the ω-(*N*-formylamino)carboxylic acids in good to high yields. This oxidation could be successfully applied to the optically active tetrahydropyridines having an oxy-functional group at the C-3 position giving the *N*-formylaminocarboxylic acids, which were converted into (3*R*)-4-amino-3-hydroxybutyric acid, an important key intermediate for the synthesis of L-carnitine. Thus, the formal asymmetric synthesis of L-carnitine was ac-

Table 1. RuO_4 Oxidation of Cyclic Ene-carbamates

Entry	Substrate	Product, isolated yield
1	 **1a**	 **1b**, 86%
2	 **2a**	 **2b**, 78%
3	 **3a**	 **3b**, 90%
4	 **4a**	 **4b**, 87%
5	 **5a**	 **5b**, 74%
6	 **6a**	 **6b**, 80%

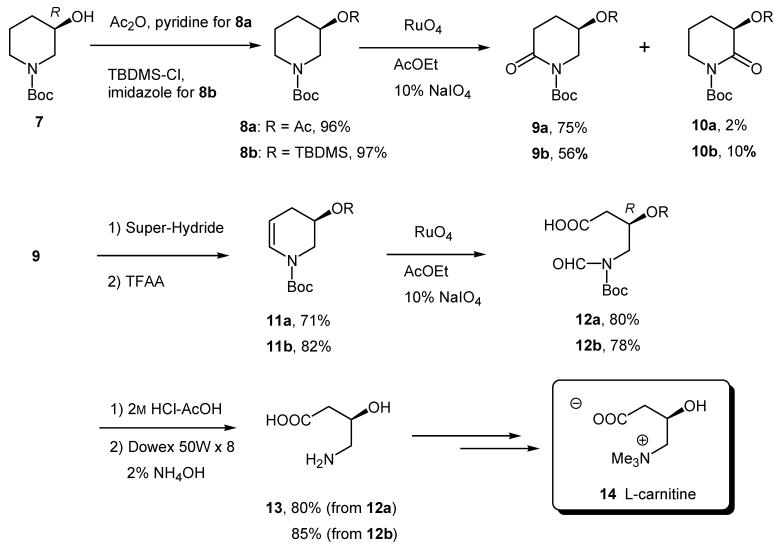


Chart 2

complished.

Experimental

General Procedures Melting points were measured on a Yanagimoto micro melting point hot stage apparatus and are uncorrected. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. IR spectra were determined with a Horiba FT-720 spectrometer. Mass spectra (MS) and HR-MS were recorded on a JEOL JMS-DX300 instrument. NMR spectra were determined with a JEOL EX-90A (90 MHz) or a JEOL JNM-GSX 400 (400 MHz) spectrometer in $CDCl_3$ or D_2O using tetramethylsilane or 1,4-dioxane (H, δ 3.70 ppm, C, δ 67.40 ppm) as internal standard and J values are given in Hz. Microanalyses were performed in the Microanalytical Laboratory in this Faculty.

Starting Cyclic Ene-carbamates Unsubstituted *N*-protected cyclic ene-carbamates (**1a**—**3a**,[19] **4a**[20—22]) were prepared by the reported method. New compounds, (**5a**,[23] **6a**[19]) were prepared from the corresponding lactams according to the procedure.

1-*tert*-Butyl 2-Methyl (2*S*)-1,2,3,4-Tetrahydropyridine-1,2-dicarboxylate (**5a**): Colorless oil; ^{1}H-NMR ($CDCl_3$) δ: 1.46 and 1.50 (9H, each s, intensity ratio 4 : 5, *t*-Bu), 1.83—2.04 and 2.24—2.39 (3H and 1H, each m, 3- and 4-H_2), 3.73 and 3.74 (3H, each s, intensity ratio 3 : 2, OMe), 4.72—4.76 and 4.79—4.84 (1H, each m, intensity ratio 2 : 3, 2-H), 4.88—4.95 (1H, m, 5-H), 6.78 and 6.91 (1H, each d, intensity ratio 3 : 2, J=8.5, 8.4 Hz, 6-H); ^{13}C-NMR ($CDCl_3$) δ: 18.32 and 18.58 (each t), 23.50 and 23.67 (each t), 28.17 and 28.26 (each q), 52.24 and 52.33 (each q), 53.16 and 54.39 (each d), 81.17 and 81.36 (each s), 104.20 and 104.64 (each d), 124.45 and 124.91 (each d), 152.28 and 152.44 (each s), 171.58 and 172.00 (each s); IR (KBr) cm^{-1}: 1753, 1709 (C=O); MS (EI) *m/z*: 241 (M^+); HR-MS *m/z*: 241.1317 (Calcd for $C_{12}H_{19}NO_4$: 241.1314); $[\alpha]_D^{21}$ −28.0 (c=1.41, $CHCl_3$).

1-*tert*-Butyl 2-(Dimethoxyphosphoryl)-2,3-dihydropyrrole-1-carboxylate (**6a**): Colorless oil; ^{1}H-NMR ($CDCl_3$) δ: 1.50 (9H, s, *t*-Bu), 2.85—3.13 (2H, m, 3-H_2), 3.78 (3H, d, $^3J_{HP}$=11.0 Hz, OMe), 3.80 (3H, d, $^3J_{HP}$=11.0 Hz, OMe), 4.43—4.61 (1H, m, 2-H), 4.98—5.14 (1H, br, 4-H), 6.34—6.64 (1H, br, 5-H); ^{13}C-NMR ($CDCl_3$) δ: 28.26 (q), 31.74 (br t), 51.61 (br d), 53.01 and 53.45 (each d_Pq, $^2J_{CP}$=6.7 Hz), 81.09 (s), 107.51 (d_Pd, $^3J_{CP}$=1.9 Hz), 130.13 (d), 151.92 (s); IR (KBr) cm^{-1}: 1703 (C=O); MS (EI) *m/z*: 277 (M^+); HR-MS *m/z*: 277.1078 (Calcd for $C_{11}H_{20}NO_5P$: 277.1079).

General Procedure for RuO_4 Oxidation of *N*-Protected Cyclic Ene-carbamates A solution of a substrate (12 mmol) to be oxidized in ethyl acetate (120 ml) was added to a mixture of $RuO_2\cdot x$hydrate (80 mg) and 10% $NaIO_4$ aqueous solution (320 ml). The reaction mixture was vigorously stirred in a sealed flask at 0 °C until disappearance of the starting materials. The layers were separated, and the aqueous layer was extracted with ethyl acetate (100 ml×3). The combined organic layer was stirred with isopropanol (2 ml) to decompose the RuO_4 for 2—3 h and filtered off. The filtrate was washed with brine (40 ml×2) and dried over anhydrous Na_2SO_4. The organic solvent was evaporated *in vacuo* to leave a residue, which was purified by silica gel chromatography using ethyl acetate–hexane (3 : 1) as an eluent to give the ω-(*N*-formylamino)carboxylic acid.

3-(*N*-*tert*-Butoxycarbonyl-*N*-formylamino)propionic Acid (**1b**): Colorless oil; ^{1}H-NMR ($CDCl_3$) δ: 1.55 (9H, s, *t*-Bu), 2.61 (2H, t, J=7.4 Hz, 2-H_2), 3.91 (2H, t, J=7.4 Hz, 3-H_2), 8.50—9.34 (2H, br, CHO and COOH); ^{13}C-NMR ($CDCl_3$) δ: 27.98 (q), 32.65 (t), 36.16 (t), 84.60 (s), 152.01 (s), 162.99 (d), 176.32 (s); IR (KBr) cm^{-1}: 3317 (OH), 1738, 1712, 1693 (C=O); MS (FAB) *m/z*: 218 (MH^+); HR-MS (FAB) *m/z*: 218.1029 (Calcd for $C_9H_{16}NO_5$: 218.1028).

4-(*N*-*tert*-Butoxycarbonyl-*N*-formylamino)butyric Acid (**2b**): Colorless oil; ^{1}H-NMR ($CDCl_3$) δ: 1.55 (9H, s, *t*-Bu), 1.82—1.96 (2H, m, 3-H_2), 2.38 (2H, t, J=7.4 Hz, 2-H_2), 3.67 (2H, J=7.1 Hz, 4-H_2), 8.42—9.49 (2H, br, CHO and COOH); ^{13}C-NMR ($CDCl_3$) δ: 23.22 (t), 27.98 (q), 31.18 (t), 39.73 (t), 84.31 (s), 152.40 (s), 163.33 (d), 178.40 (s); IR (KBr) cm^{-1}: 3201 (OH), 1738, 1705, 1693 (C=O); MS (FAB) *m/z*: 232 (MH^+); HR-MS (FAB) *m/z*: 232.1088 (Calcd for $C_{10}H_{18}NO_5$: 232.1185).

5-(*N*-*tert*-Butoxycarbonyl-*N*-formylamino)pentanoic Acid (**3b**): Colorless oil; ^{1}H-NMR ($CDCl_3$) δ: 1.55 (9H, s, *t*-Bu), 1.57—1.69 (4H, m, 3- and 4-H_2), 2.39 (2H, t, J=7.1 Hz, 2-H_2), 3.61 (2H, J=6.9 Hz, 5-H_2), 8.75—11.30 (2H, br, CHO and COOH); ^{13}C-NMR ($CDCl_3$) δ: 21.80 (t), 27.65 (t), 28.02 (q), 33.50 (t), 40.04 (t), 84.11 (s), 152.48 (s), 163.25 (d), 179.15 (s); IR (KBr) cm^{-1}: 3224 (OH), 1736, 1705, 1691 (C=O); MS (FAB) *m/z*: 246 (MH^+); HR-MS (FAB) *m/z*: 246.1344 (Calcd for $C_{11}H_{20}NO_5$: 246.1341).

(2*S*)-2-(*N*-*tert*-Butoxycarbonyl-*N*-formylamino)succinic Acid 1-Methyl Ester (**4b**): Colorless oil; ^{1}H-NMR ($CDCl_3$) δ: 1.54 (9H, s, *t*-Bu), 2.75 and 3.31 (each 1H, dd, J=16.9, 6.6 and 16.9, 7.3 Hz, 3-H_2), 3.74 (3H, s, COOMe), 5.52 (1H, dd, J=7.3, 6.6 Hz, 2-H), 7.28 (1H, br s, CHO), 9.16 (1H, s, COOH); ^{13}C-NMR ($CDCl_3$) δ: 27.93 (q), 34.53 (t), 49.26 (d), 52.86 (q), 85.55 (s), 151.30 (s), 162.23 (d), 169.20 (s), 175.27 (s); IR (KBr) cm^{-1}: 3452 (OH), 1747, 1712, 1699 (C=O); MS (FAB) *m/z*: 276 (MH^+); HR-MS (FAB) *m/z*: 276.1082 (Calcd for $C_{11}H_{18}NO_7$: 276.1083); $[\alpha]_D^{21}$ −75.9 (c=1.0, $CHCl_3$).

(2*S*)-2-(*N*-*tert*-Butoxycarbonyl-*N*-formylamino)pentanedioic Acid 1-Methyl Ester (**5b**): Colorless oil; ^{1}H-NMR ($CDCl_3$) δ: 1.52 (9H, s, *t*-Bu), 2.14—2.25 and 2.33—2.55 (1H and 3H, each m, 3- and 4-H_2), 3.73 (3H, s, OMe), 5.05 (1H, dd, J=9.7, 5.0 Hz, 2-H), 7.45—8.98 (1H, br, COOH), 9.22 (1H, s, CHO); ^{13}C-NMR ($CDCl_3$) δ: 24.09 (t), 27.91 (q), 30.46 (t), 52.14 (d), 52.51 (q), 85.30 (s), 151.55 (s), 162.80 (d), 169.77 (s), 178.09 (s); IR (KBr) cm^{-1}: 3384 (OH), 1743, 1711 (C=O); MS (FAB) *m/z*: 290 (MH^+). HR-MS (FAB) *m/z*: 290.1242 (Calcd for $C_{12}H_{20}NO_7$: 290.1240); $[\alpha]_D^{21}$ −30.5 (c=6.4, MeOH).

3-(*N*-*tert*-Butoxycarbonyl-*N*-formylamino)-3-(dimethoxyphosphoryl)propionic Acid (**6b**): Colorless oil; ^{1}H-NMR ($CDCl_3$) δ: 1.56 (9H, s, *t*-Bu), 2.79—3.01 and 3.06—3.28 (each 1H, m, 2-H_2), 3.75 and 3.82 (each 3H, d, $^3J_{HP}$=11.0 Hz, OMe×2), 5.06—5.45 (1H, m, 3-H), 9.13 (1H, s, CHO), 9.16—9.45 (1H, br, COOH); ^{13}C-NMR ($CDCl_3$) δ: 27.88 (q), 32.53 (t), 43.11 (d_Pd, $^1J_{CP}$=149.5 Hz), 53.09 and 55.21 (each d_Pq, $^2J_{CP}$=6.7 Hz), 85.45 (s), 151.52 (s), 162.67 (d), 172.77 (d_P, $^3J_{CP}$=16.3 Hz); IR (KBr) cm^{-1}: 3423 (OH), 1699 (C=O); MS *m/z*: 326 (MH^+); HR-MS (FAB) *m/z*: 326.1008 (Calcd for $C_{11}H_{21}NO_8P$: 326.1005).

***tert*-Butyl (3*R*)-3-Hydroxypiperidine-1-carboxylate (7)** This compound was synthesized by the reported method.[27] Colorless oil; $[\alpha]_D^{20}$ −10.8 (c=1.11, $CHCl_3$); lit.[27] $[\alpha]_D^{20}$ −9.6 (c=1, $CHCl_3$).

***tert*-Butyl (3*R*)-3-Acetoxypiperidine-1-carboxylate (8a)** Ac_2O (3.67 g, 36 mmol) was slowly added to a solution of **7** (6.04 g, 30 mmol) in pyridine (50 ml) with stirring at 0 °C. The reaction mixture was allowed to warm to room temperature, stirred for 24 h. The mixture was diluted with benzene (300 ml) and saturated aqueous $NaHCO_3$ (150 ml). The organic layer was washed with water (50 ml×3), dried over anhydrous Na_2SO_4, and evaporated to furnish the crude product which was purified by chromatography (silica gel, AcOEt–hexane, 1 : 5). 7.04 g (96%); colorless oil; $[\alpha]_D^{20}$ +22.6 (c=2.46, $CHCl_3$); lit.[27] $[\alpha]_D^{20}$ +21.2 (c=1.1, $CHCl_3$). This compound was identical with the authentic sample prepared in the previous paper.[27]

***tert*-Butyl (3*R*)-3-(*tert*-Butyldimethylsilyloxy)piperidine-1-carboxylate (8b)** *tert*-Butyldimethylsilyl chloride (5.65 g, 37.5 mmol) was slowly added to a solution of **7** (6.04 g, 30 mmol) and imidazole (8.17 g, 120 mmol) in dry DMF (50 ml) with stirring at 0 °C. The reaction mixture was allowed to warm to room temperature, stirred for 24 h, and poured into ice-water (100 ml). The aqueous mixture was extracted with AcOEt (100 ml×3), organic layer was washed with brine (50 ml×3), dried over anhydrous Na_2SO_4, and evaporated to furnish the crude product which was purified by chromatography (silica gel, AcOEt–hexane, 1 : 5). 9.22 g (97%); colorless oil; ^{1}H-NMR ($CDCl_3$) δ: 0.07 and 0.08 (each 3H, s, $SiMe_2$), 0.89 (9H, s, Si*t*-Bu), 1.45 (9H, s, COO*t*-Bu), 1.35—1.52 (2H, m, 5-H_2), 1.66—1.76 and 1.80—1.90 (each 1H, m, 4-H_2), 2.70—2.97 (2H, m, 6-H_2), 3.53—3.94 (3H, m, 2-H_2 and 3-H); ^{13}C-NMR ($CDCl_3$) δ: −4.74 (q), 18.13 (s), 23.04 (t), 25.82 (q), 28.44 (q), 33.90 (t), 43.36 and 44.10 (t), 50.51 and 51.54 (t), 67.14 (d), 79.30 (s), 154.78 (s); IR (KBr) cm^{-1}: 1699 (C=O); MS (FAB) *m/z*: 316 (MH^+); HR-MS (FAB) *m/z*: 316.2313 (Calcd for $C_{16}H_{34}NO_3Si$: 316.2308); $[\alpha]_D^{20}$ −14.1 (c=1.31, $CHCl_3$).

RuO_4 Oxidation of *N*-Boc-piperidines (8) A solution of piperidine (**8**, 24 mmol) was oxidized in ethyl acetate (80 ml) was added to a mixture of $RuO_2\cdot x H_2O$ (200 mg) and 10% aqueous $NaIO_4$ solution (240 ml). The reaction mixture was stirred in a sealed flask at 20 °C until disappearance of the starting material, and worked up as described above for the general procedure for RuO_4 oxidation of *N*-protected cyclic ene-carbamates, and the 3-substituted 2-oxopiperidines (**10**, the first fractions) and 5-substituted 2-oxo derivatives (**9**, the second fractions) could be separated by silica gel chromatography.

tert-Butyl (5*R*)-5-Acetoxy-2-oxopiperidine-1-carboxylate (**9a**): 4.63 g (75%); colorless oil; ^{1}H-NMR ($CDCl_3$) δ: 1.53 (9H, s, *t*-Bu), 1.95—2.08 and 2.11—2.18 (each 1H, m, 4-H_2), 2.08 (3H, s, OAc), 2.47—2.55 and 2.61—2.69 (each 1H, m, 3-H_2), 3.72 and 3.93 (each 1H, dd and ddd, J=14.0, 3.8 and 14.0, 4.0, 1.6 Hz, 6-H_2), 5.18—5.24 (1H, m, 5-H); ^{13}C-NMR ($CDCl_3$) δ: 21.07 (q), 25.26 (t), 27.98 (q), 31.03 (t), 49.02 (t), 66.20 (d), 83.35 (s), 152.01 (s), 170.19 (s), 170.20 (s); IR (KBr) cm^{-1}: 1774, 1738, 1722 (C=O); MS (FAB) *m/z*: 258 (MH^+). HR-MS (FAB) *m/z*: 258.1339 (Calcd for $C_{12}H_{20}NO_5$: 258.1342); $[\alpha]_D^{25}$ +13.0 (c=1.5, $CHCl_3$).

tert-Butyl (3*R*)-3-Acetoxy-2-oxopiperidine-1-carboxylate (**10a**): 124 mg (2%), colorless oil; ^{1}H-NMR ($CDCl_3$) δ: 1.52 (9H, s, *t*-Bu), 1.86—2.04 and 2.20—2.29 (3H and 1H, each m, 4- and 5-H_2), 2.16 (3H, s, OAc), 3.60—

3.67 and 3.76—3.84 (each 1H, m, 6-H_2), 5.31 (1H, dd, J=10.8, 7.3 Hz, 3-H); ^{13}C-NMR ($CDCl_3$) δ: 20.27 (t), 20.81 (q), 26.23 (t), 27.97 (q), 44.86 (t), 69.99 (d), 83.40 (s), 152.43 (s), 168.00 (s), 169.96 (s); IR (KBr) cm^{-1}: 1776, 1738, 1722 (C=O); MS (EI) *m/z*: 257 (M^+). HR-MS (EI) *m/z*: 257.1258 (Calcd for $C_{12}H_{19}NO_5$: 257.1263); $[\alpha]_D^{25}$ +51.4 (c=1.1, $CHCl_3$).

tert-Butyl (5*R*)-5-(*tert*-Butyldimethylsilyloxy)-2-oxopiperidine-1-carboxylate (**9b**): 4.42 g (56%); colorless oil; ^{1}H-NMR ($CDCl_3$) δ: 0.09 (6H, s, $SiMe_2$), 0.89 (9H, s, Si*t*-Bu), 1.52 (9H, s, COO*t*-Bu), 1.79—1.88 and 1.92—2.01 (each 1H, m, 4-H_2), 2.39—2.47 and 2.67—2.76 (each 1H, m, 3-H_2), 3.60—3.72 (2H, m, 6-H_2), 4.13—4.19 (1H, m, 5-H); ^{13}C-NMR ($CDCl_3$) δ: −4.88 (q), 17.99 (s), 25.68 (q), 28.00 (q), 29.00 (t), 31.06 (t), 52.42 (t), 64.44 (d), 82.83 (s), 152.49 (s), 170.90 (s); IR (KBr) cm^{-1}: 1774, 1716 (C=O); MS (FAB) *m/z*: 330 (MH^+). HR-MS (FAB) *m/z*: 330.2103 (Calcd for $C_{16}H_{32}NO_4Si$: 330.2101); $[\alpha]_D^{24}$ −8.1 (c=0.95, $CHCl_3$).

tert-Butyl (3*R*)-3-(*tert*-Butyldimethylsilyloxy)-2-oxopiperidine-1-carboxylate (**10b**): 0.79 g (10%); colorless oil; ^{1}H-NMR ($CDCl_3$) δ: 0.15 and 0.17 (6H, each s, intensity ratio 9 : 11, $SiMe_2$), 0.90 and 0.91 (9H, each s, intensity ratio 4 : 5, Si*t*-Bu), 1.51 and 1.56 (9H, each s, intensity ratio 4 : 5, COO*t*-Bu), 1.71—2.13 (4H, m, 4- and 5-H_2), 6-H_2 [2.57—2.66 and 2.84—2.93 (1H, each m, intensity ratio 2 : 3), 3.58—3.72 (1H, m)], 4.17 and 4.33 (1H, each dd, intensity ratio 2 : 3, J=8.2, 5.6 and 7.4, 4.6 Hz, 3-H); ^{13}C-NMR ($CDCl_3$) δ: −5.56, −5.41, −4.77 and −4.59 (each q), 18.22 and 18.32 (each s), 19.91 and 26.56 (each t), 25.63 and 25.77 (each q), 27.46 and 28.00 (each q), 28.70 and 30.46 (each t), 45.54 (t), 68.74 and 71.54 (each d), 82.72 and 86.31 (each s), 148.61 and 152.74 (each s), 169.63 and 171.98 (each s); IR (KBr) cm^{-1}: 1778, 1707 (C=O); MS (FAB) *m/z*: 330 (MH^+). HR-MS (FAB) *m/z*: 330.2102 (Calcd for $C_{16}H_{32}NO_4Si$: 330.2101); $[\alpha]_D^{24}$ +16.2 (c=1.02, $CHCl_3$).

***tert*-Butyl (3*R*)-3-Acetoxy-1,2,3,4-tetrahydropyridine-1-carboxylate (11a)** To a solution of the lactam (**9**, 2.57 g, 10 mmol) in toluene (20 ml) at −70 °C Super-Hydride (1.0 M in THF, 10.6 ml) was added dropwise. After stirring at −70 °C for 30 min, DIPEA (10 ml, 57 mmol), dimethylaminopyridine (24 mg) and TFAA (1.7 ml, 12 mmol) were added. The mixture was warmed to room temperature and stirred for 2 h, and water (20 ml) was added to the mixture. Organic layer was separated and washed with brine (30 ml×3), dried over anhydrous Na_2SO_4, and evaporated to furnish the crude product which was purified by chromatography (silica gel, AcOEt–hexane, 1 : 5). 1.71 g (71%); colorless oil; ^{1}H-NMR ($CDCl_3$) δ: 1.47 and 1.49 (9H, each s, intensity ratio 4 : 6, *t*-Bu), 2.06 (3H, s, OAc), 2.12—2.18 and 2.36—2.43 (each 1H, m, 4-H_2), 3.56—3.74 (2H, m, 2-H_2), 4.69—4.87 (1H, m, 3-H), 5.08—5.21 (1H, br, 5-H), 6.76 and 6.88 (1H, each d, intensity ratio 3 : 2, J=8.2 and 7.1 Hz, 6-H); ^{13}C-NMR ($CDCl_3$) δ: 21.17 (q), 27.22 and 27.35 (each t), 28.28 (q), 44.15 and 45.14 (t), 65.76 and 65.92 (each d), 81.08 (s), 101.27 and 101.73 (each d), 125.42 and 125.77 (each d), 152.35 and 152.67 (each s), 170.40 (s); IR (KBr) cm^{-1}: 1739, 1705 (C=O); MS (EI) *m/z*: 241 (M^+). HR-MS (EI) *m/z*: 241.1312 (Calcd for $C_{12}H_{19}NO_4$: 241.1314); $[\alpha]_D^{23}$ +18.4 (c=1.06, $CHCl_3$).

***tert*-Butyl (3*R*)-3-(*tert*-Butyldimethylsilyloxy)-1,2,3,4-tetrahydropyridine-1-carboxylate (11b)** This compound was prepared from **9b** in a similar manner to that described for **11a**. 2.57 g (82%); colorless oil; ^{1}H-NMR ($CDCl_3$) δ: 0.08 and 0.09 (each 3H, s, $SiMe_2$), 0.88 (9H, s, Si*t*-Bu), 1.49 (9H, s, COO*t*-Bu), 1.96—2.06 and 2.19—2.29 (each 1H, m, 4-H_2), 2-H_2 [3.06—3.19 (1H, m), 3.73 and 3.84 (1H, each d, intensity ratio 3 : 7, J=11.7 and 12.0 Hz)]. 3.95—4.04 (1H, m, 3-H), 4.66—4.88 (1H, m, 5-H), 6.67 and 6.81 (1H, each d, intensity ratio 7 : 3, J=8.1 and 7.8 Hz, 6-H); ^{13}C-NMR ($CDCl_3$) δ: −4.76 and −4.68 (each q), 18.06 and 18.12 (each s), 25.78 (q), 28.32 (q), 31.71 and 31.85 (each t), 47.54 and 48.72 (each t), 64.83 (d), 80.56 and 80.69 (each s), 102.37 and 102.94 (each d), 125.08 and 125.40 (each d), 152.29 and 152.65 (each s); IR (KBr) cm^{-1}: 1705 (C=O); MS (EI) *m/z*: 313 (M^+); HR-MS (EI) *m/z*: 313.2070 (Calcd for $C_{16}H_{31}NO_3Si$: 313.2073); $[\alpha]_D^{25}$ −16.5 (c=1.18, $CHCl_3$).

(3*R*)-3-Acetoxy-4-(*N*-*tert*-butoxycarbonyl-*N*-formylamino)butyric Acid (12a) The enamine (**11**, 24 mmol) was oxidized and worked up as described above for the general procedure for RuO_4 oxidation of *N*-protected cyclic ene-carbamates. 5.57 g (80%); colorless oil; ^{1}H-NMR ($CDCl_3$) δ: 1.56 (9H, s, *t*-Bu), 2.01 (3H, s, OAc), 2.64 (2H, d, J=6.7 Hz, 2-H_2), 3.81 and 3.95 (each 1H, dd, J=14.2, 3.8 and 14.2, 6.9 Hz, 4-H_2), 5.42—5.48 (1H, m, 3-H), 6.81—7.28 (1H, br, COOH), 9.17 (1H, s, CHO); ^{13}C-NMR ($CDCl_3$) δ: 20.87 (q), 27.95 (q), 36.75 (t), 42.47 (t), 67.90 (d), 84.87 (s), 152.13 (s), 163.44 (d), 170.53 (s), 174.48 (s); IR (KBr) cm^{-1}: 3482 (OH), 1743, 1711, 1693 (C=O); MS (FAB) *m/z*: 290 (MH^+). HR-MS (FAB) *m/z*: 290.1242 (Calcd for $C_{12}H_{20}NO_7$: 290.1240); $[\alpha]_D^{23}$ +10.0 (c=1.99, $CHCl_3$).

(3*R*)-4-(*N*-*tert*-Butoxycarbonyl-*N*-formylamino)-3-(*tert*-butyldimethylsilyloxy)Butyric Acid (12b) 6.77 g, (78%); colorless oil; ^{1}H-NMR ($CDCl_3$) δ: 0.06 and 0.08 (each 3H, s, $SiMe_2$), 0.86 (9H, s, Si*t*-Bu), 1.55 (9H, s, COO*t*-Bu), 2.49 (2H, d, J=6.4 Hz, 2-H_2), 3.63 and 3.78 (each 1H, dd, J=13.6, 6.7 Hz and 13.5, 6.6 Hz, 4-H_2), 4.30—4.38 (1H, m, 3-H), 9.19 (1H, s, CHO), 9.28—10.12 (1H, br, COOH); ^{13}C-NMR ($CDCl_3$) δ: −5.10 and −4.59 (each s), 17.83 (s), 25.68 (q), 28.06 (q), 40.79 (t), 45.53 (t), 66.59 (d), 84.53 (s), 152.33 (s), 163.32 (d), 176.54 (s); IR (KBr) cm^{-1}: 3174 (OH), 1741, 1712, 1697 (C=O); MS (FAB) *m/z*: 362 (MH^+); HR-MS (FAB) *m/z*: 362.2002 (Calcd for $C_{16}H_{32}NO_6Si$: 362.1999); $[\alpha]_D^{26}$ −3.5 (c=1.02, $CHCl_3$).

(3*R*)-4-Amino-3-hydroxybutyric Acid (13) A mixture of the imide (**12a**, 1 mmol) in 2 M HCl (4 ml) and AcOH (4 ml) was heated at 60 °C under argon atmosphere for 12 h, and concentrated *in vacuo*. The obtained residue was desalted by ion-exchange chromatography on a Dowex 50W×8 (50—100 mesh, 38 ml, H^+ form) column with 2% NH_4OH. Concentration of elute to dryness to give the crude *ω*-acid, which was recrystallized from water–EtOH. 96 mg (80% from **12a**); colorless prisms, mp 211 °C (lit.[28] mp 211—213 °C); ^{1}H-NMR (D_2O) δ: 2.38 (2H, d, J=6.5 Hz, 2-H_2), 2.91 and 3.12 (each 1H, dd, J=13.1, 9.4 Hz and 13.1, 3.2 Hz, 4-H_2), 4.11—4.21 (1H, m, 3-H); ^{13}C-NMR (D_2O) δ: 43.19 (t), 44.99 (t), 66.39 (d), 179.42 (s); IR (KBr) cm^{-1}: 3413 (OH, NH), 1577 (C=O); MS (FAB) *m/z*: 120 (MH^+); $[\alpha]_D^{25}$ −21.1 (c=0.79, H_2O)(lit.[28] $[\alpha]_D^{28}$ −20.7 (c=1.0, H_2O)). 102 mg (85% from **12b**).

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